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Sprague-Dawley rats were exposed to 2450-MHz microwaves at an average power density of 60 mW/cm^2 until lethal temperatures were attained. The effects of propanolol, nadolol, and labetalol on physiological responses were examined. Lethal temperatures in the labetalol and both propanolol groups were significantly lower than in saline controls. Respiratory rate was significantly elevated during most of the exposure period in animals given the high dose of propranolol. This respiration change is consistent with other studies of adrenergic blockade and may have been related to the shorter survival time in these animals.

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Cardiorespiratory changes during microwave-induced lethal heat stress and β-adrenergic blockade

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Jauchem, James R., and Melvin R. Frei. Cardiorespiratory changes during microwave-induced lethal heat stress and β-adrenergic blockade. *J. Appl. Physiol.* 77(1): 434–440, 1994.— Ketamine-anesthetized Sprague-Dawley rats were exposed to 2,450-MHz microwaves at an average power density of 60 mW/cm^2 (whole body specific absorption rate of ~14 W/kg) until lethal temperatures were attained. The effects of propranolol (2 or 10 mg/kg body wt), nadolol (10 mg/kg), and labetalol (10 mg/kg) on physiological responses (including changes in body temperature, heart rate, blood pressure, and respiratory rate) were examined. Lethal temperatures in the labetalol and both propranolol groups were significantly lower than in saline controls. Survival time was significantly less only in the high-dose propranolol group. In all groups, heart rate increased continuously during exposure; blood pressure increased until colonic temperature reached 41–41.5°C and then decreased. These heart rate and blood pressure changes were similar to those that occur during environmental heat stress. Heart rate and blood pressure changes among groups were similar. Respiratory rate, however, was significantly elevated during most of the exposure period in the high-dose propranolol animals. This change in respiration, coupled with the significantly lower survival time in these animals, suggests a vital role of respiration in susceptibility to microwave-induced heating.

radio-frequency radiation; body temperature; heart rate; blood pressure; respiration; thermal stress

THE MILITARY AND CIVILIAN use of microwave radiation (MW) has steadily increased since the 1940s. Although studies of MW bioeffects and speculations on mechanisms of effect are numerous, it appears that an increase in body temperature is the primary effect of exposure to high levels of MW (19).

Although temperature gradients are normally present in the mammalian body, core-to-skin thermal differences are often assumed to be minimal in studies of environmental heating. During MW exposures, however, particularly at high frequencies, relatively large thermal gradients may exist. The depth of penetration is greater at lower frequencies. At high frequencies (such as 2,450 MHz), surface heating occurs more rapidly than internal heating.

Kregel and Gisolfi (27) have definitively described the cardiovascular and peripheral vascular responses to hyperthermia in the rat. In general, cardiovascular and respiratory responses to environmental heating and MW-induced heating appear to be similar. Some quantitative differences in the magnitude of changes may occur because of differences in thermal gradients within the body resulting from the two types of heating (19).

Wenger (43) has suggested that basic studies of cardiovascular responses might be easier to perform with MW-induced heating than with conventional methods. In addition to basic research applications, heating with radiofrequency radiation at lower frequencies is being investigated as a means of therapy for accidental hypothermia.

Although several studies have determined mortality rates and lethal power densities for animals exposed to MW (e.g., Ref. 35), few investigations have included measurements of physiological changes (such as cardiovascular and respiratory changes) during lethal exposures. Although the pathophysiology of heatstroke has been studied extensively, the mechanisms responsible for death due to heat exposure and the effects of drugs on heat tolerance remain as high priorities for research.

Selection of the proper animal model for thermoregulatory studies is critical. Guyton (12) reported that cardiac output regulation in laboratory rats is qualitatively and quantitatively identical to that in humans. Heat-induced mortality curves are also similar between rats and humans (14). The value of the anesthetized rat as a model for studying heat stress responses has been addressed previously by Kielblock et al. (26) and Kregel et al. (28). It is important to note that cardiovascular responses to heat stress generally persist in anesthetized animal models (5).

Objective data concerning the effect of adrenergic receptor blockade on thermoregulatory responses to environmental heat exposure (or to exercise resulting in metabolic heat production) are scarce and conflicting. Some studies have reported a marked rise in rectal temperature, whereas others have shown no changes, after β-adrenergic receptor antagonism. During β-adrenergic blockade, impaired skin blood perfusion might be expected to hinder the elimination of heat. Pescatello et al. (34) noted that acute intake of the β-adrenergic receptor antagonist propranolol in humans resulted in a diminished transfer of heat from body core to skin, resulting in an elevated core temperature.

In an earlier study, during terminal exposure to 2.8-GHz MW (60 mW/cm^2; whole body average specific absorption rate, 14 W/kg), anesthetized propranolol-treated (5 mg/kg) animals exhibited decreased survival times and significantly lower lethal colonic temperatures (T_c) compared with saline-treated animals (20). In contrast to propranolol, which readily enters the central nervous system, the β-adrenergic receptor antagonist nadolol is not very lipid soluble and has a poor ability to traverse the blood-brain barrier. Only minimal amounts of nadolol have been detected in the brain relative to amounts found in other body fluids and tissues. By comparing effects of nadolol (essentially a "peripheral" blocking agent) with those of propranolol (with both

"central" and peripheral activity), it may be possible to differentiate between central and peripheral mechanisms of thermoregulation.

α_1-Adrenergic blockade has been shown to affect thermoregulation. Labetalol is a unique agent that combines both selective α_1- and nonselective β-blocking activity. The drug can cause decreases in body temperature of the rat (6). In contrast to pure β-blocking agents, labetalol has a tendency to preserve blood perfusion in some areas of the body.

The purpose of this study was twofold: 1) to characterize heart rate (HR), arterial blood pressure, respiratory rate (RR), and localized body temperature changes that occur during lethal exposure of anesthetized rats to 2,450 MHz MW and 2) to examine the effects of propranolol, nadolol, and labetalol on these responses as well as on survival times and lethal temperatures. On the basis of previous studies, we hypothesized that propranolol would decrease lethal temperature and survival time. If these changes are due to predominantly central (as opposed to peripheral) β-adrenergic antagonism, then nadolol would have less of an effect. Because labetalol causes a decrease in body temperature, administration of the drug could result in an increase in survival time during lethal heat stress.

MATERIALS AND METHODS

Animals and physiological monitoring. Forty-two male Sprague-Dawley CD-VAF/Plus rats (Charles River Laboratories, Wilmington, MA), weighing between 320 and 363 g [mean 350 ± 2 (SE) g], were used in this study. Formal approval was received from the Armstrong Laboratory Animal Use Committee to conduct these experiments. The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Resources of the National Research Council. Before experimentation, animals were housed in polycarbonate cages with free access to food and water and maintained on a 12:12-h light-dark cycle (lights on at 0600 h) in a climatically controlled environment (ambient temperature 24 ± 1°C).

Animals were fasted for 18 h (water ad libitum) before experimentation. Ketamine HCl (Vetalar; 150 mg/kg im) was administered as a general anesthetic, with supplemental doses provided as necessary during experimentation. Administration of ketamine at approximately this dose provides adequate anesthesia in Sprague-Dawley rats and results in a stable animal preparation compatible with physiological monitoring (9). The anesthetic has minimal effects on temperature regulation in rats (36) and is known for its lack of significant autonomic, cardiovascular, or respiratory effects. Ketamine preserves cardiovascular function better than other anesthetics (37) during compromised situations such as experimental shock and results in a more stable distribution of cardiac output to splanchnic organs. Ketamine also does not impair tissue oxygenation during conditions of compromised circulation (13).

The left carotid artery was catheterized for measurement of mean arterial blood pressure (MAP). Immediately after surgery, the animal was placed on a holder in the MW exposure chamber. The holder consisted of seven 0.5-cm-OD Plexiglas rods mounted in a semicircular pattern on 4 × 6-cm Plexiglas plates (0.5 cm thick). The catheter was attached to a precalibrated blood pressure transducer (Century CP-01) that was interfaced with a pressure processor (Gould 13–4615–52) to give permanent records via a Gould 2600S recorder. To determine

HR, a lead II electrocardiogram was obtained by use of nylon-covered fluorocarbon leads attached to shielded cables outside the MW field. RR was monitored by a pneumatic transduction method employing a piezoelectric pressure transducer (model 320–0102-B, Narco Biosystems). A detailed description of these techniques has been reported previously (10).

Temperature was monitored at four sites on each rat: 1) colonic (5–6 cm postanus), 2) right tympanic, 3) left subcutaneous (lateral, midthoracic, side facing the antenna), and 4) right subcutaneous (lateral, midthoracic, side away from MW source. The temperatures were monitored with BSD thermister probes, which were attached to a BSD-200 Precision Thermometry System (BSD Medical) to obtain continuous (12-s sampling interval) temperature readings.

MW equipment. The continuous-wave MW fields were produced by a model 1325 MW power source (Cober Electronics) and transmitted by a model 644 antenna (Narda Microwave). The exposures were performed under far-field conditions (animal positioned on boresight 115 cm from antenna), and the incident power of the field was determined with an electromagnetic radiation monitor (model 8616, Narda Microwave), employing a model 8623 probe. During exposures, the generator power was monitored constantly with a model 432-B power meter (Hewlett-Packard). Irradiation was conducted in a Eccosorb MW-shielded anechoic chamber (Rantec, Emerson Electric). The temperature and relative humidity in the chamber were held constant for all experiments (27 ± 0.5°C, 20 ± 5% relative humidity).

Exposure conditions. The animals were exposed individually, in H orientation (left lateral exposure, long axis of body parallel to magnetic field), to far-field 2.45-GHz continuous-wave MW (average power density of 60 mW/cm²). This exposure resulted in a whole body average specific absorption rate of 14 W/kg, determined calorimetrically by methods reported previously (9). Because each animal exhibited a different starting T_c, an initial MW exposure was performed to increase T_c to a standard level: in this case, 39.5°C. This temperature was selected for several reasons. Our previous studies had shown that responses to MW exposure are more stable and reproducible at T_c of 38.5°C and above. When T_c reached 39.5°C, MW exposure was temporarily halted, allowing personnel access to the exposure chamber to administer the antagonist. Injection of the antagonist during the T_c drop from 39.5 to 38.5°C allowed for initiation of blockade before the final lethal exposure to MW at 38.5°C was started.

Propranolol (Inderal; 2 or 10 mg/kg), nadolol (Corgard; 10 mg/kg), or labetalol (Normodyne; 10 mg/kg) was administered intraperitoneally at a volume of 2.0 ml/kg body wt. A series of control animals received an identical volume of saline. Because our previous studies had shown significant effects of propranolol, we compared two different doses of the drug in the present experiments. The intraperitoneal injections were given in the left caudal quadrant of the abdomen to lessen the chances of inadvertent injection outside the peritoneal cavity. After T_c returned to 38.5°C, exposure to MW was performed until a lethal temperature was attained. [The lethal event in hyperthermia due to both MW (23) and environmental heating (4) is cessation of respiration.] Survival times and temperatures at which death occurred were recorded. Because this study focused on MW-induced heating, the physiological data (HR, RR, and MAP) were plotted as a function of temperature change rather than duration of exposure.

Statistical analysis. Data are presented as group means ± SE. Analysis of variance was applied to determine if there were significant differences between group means obtained in the different drug treatment and saline-injected groups. If statistical differences were found by analysis of variance, the Tukey honestly significant test for unequal sample sizes (Spjøtvoll

and Stoline test) was used to identify pairs of group means that were significantly different. For HR, MAP, and RR data, statistical analyses were performed on changes from the values obtained at 38.5°C in each group in addition to absolute values. A P value of <0.05 was considered to indicate significance in all cases.

RESULTS

The times required for T_c to drop from 39.5 to 38.5°C after drug administration were as follows: saline ($n = 9$), 24.5 ± 2.1 (SE); nadolol ($n = 7$), 22.2 ± 2.3; 2 mg/kg propranolol ($n = 9$), 19.0 ± 2.5; 10 mg/kg propranolol ($n = 10$), 18.8 ± 2.3; and labetalol ($n = 7$), 23.5 ± 2.8 min. There were no significant differences among these values.

Values of lethal T_c were as follows: saline, 43.6 ± 0.1; 2 mg propranolol, 43.1 ± 0.2; 10 mg propranolol, 43.1 ± 0.1; nadolol, 43.7 ± 0.2; and labetalol, 43.2 ± 0.2°C (Fig. 1). Lethal temperatures in the labetalol and both propranolol groups were significantly lower than that in the saline group. Temperatures in the two propranolol groups were also significantly lower than that in the nadolol group. Survival times (time from T_c of 38.5°C until death) were 34.5 ± 0.7, 34.2 ± 2.2, 27.9 ± 0.7, 32.3 ± 0.9, and 37.5 ± 1.9 min in these groups, respectively (Fig. 2). Survival time in only the high-dose propranolol group was significantly less than in the saline group; it was also significantly less than the times in the low-dose propranolol and labetalol groups.

The rates of increase in T_c during MW exposure were 0.16 ± 0.004 (saline), 0.15 ± 0.01 (2 mg propranolol), 0.16 ± 0.004 (10 mg propranolol), 0.16 ± 001 (nadolol), and 0.13 ± 0.005°C/min (labetalol). The rate of temperature rise in the labetalol group was significantly less than those in the high-dose propranolol and nadolol groups.

Initial and terminal values of tympanic and right and left subcutaneous temperatures are given in Table 1. There were no significant differences in initial temperatures at any of the sites among the different groups of animals. The increase in left subcutaneous temperature
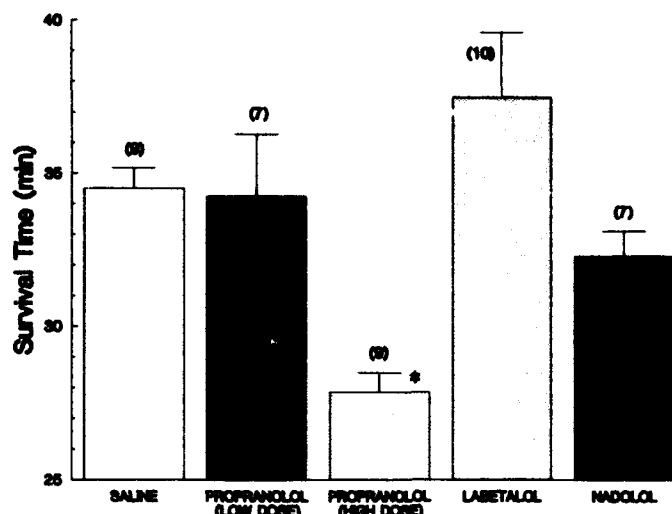
FIG. 2. Effects of adrenergic blocking agents on survival time during terminal exposure to microwaves. Values are means ± SE. Nos. of animals in each group are given in parentheses. * Significantly different from results in saline-treated animals.

was significantly greater in the nadolol group than in the low-dose propranolol group.

HR changes, recorded at each 0.5°C of T_c change, are illustrated in Fig. 3. HR increased in each group during MW exposure. During the period immediately after drug administration (from T_c of 39.5 to 38.5°C, with MW off), HR decreased in each group. Although there were no significant differences among the absolute values at any temperature in the various groups, the change in HR immediately after drug administration (the decrease at 39.5°C relative to the value at 38.5°C in each respective group) was significantly greater in the two propranolol groups than in the saline group. HR in the labetalol and nadolol groups also decreased to a greater extent than in the saline group, but the changes were not statistically significant. During terminal exposure, a continuous rise in HR occurred in each group throughout the exposure period. There were no significant differences among the absolute values nor among the changes in the groups during the terminal exposure.

After drug administration (from T_c of 39.5 to 38.5°C), MAP decreased in each group (Fig. 4). During terminal exposure, in general, MAP increased until T_c reached 41.0 or 41.5°C and then decreased while exposure continued. At 41.5°C, animals in the low-dose propranolol group exhibited a significantly larger decrease (relative to value at 38.5°C) than animals in the high-dose propranolol group. At 42.5 and 43.0°C, the drop in MAP in the low-dose propranolol group was significantly greater than the decreases in the saline and nadolol groups. The decrease in the high-dose propranolol group was significantly greater at 42.5°C than that in the nadolol group. Despite these differences in changes relative to values at the start of terminal exposure, there were no significant differences in absolute values among the various groups at any point.

At T_c from 39.5 to 42.0°C during terminal exposure, RR in the high-dose propranolol group was significantly greater than RR in all but the nadolol group (Fig. 5). At
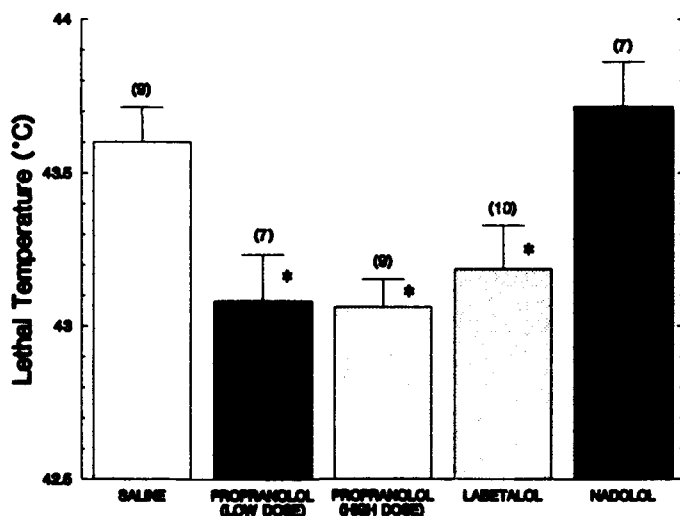
FIG. 1. Effects of adrenergic blocking agents on lethal colonic temperature during terminal exposure to microwaves. Nos. of animals in each group are given in parentheses. * Significantly different from results in saline-treated animals.

TABLE 1. *Initial and terminal temperatures*

	Tympanic		Left Subcutaneous		Right Subcutaneous	
	Initial	Terminal	Initial	Terminal	Initial	Terminal
Saline	38.4±0.1	43.6±0.2	37.5±0.5	43.3±0.5	38.2±0.1	42.5±0.1
Propranolol (2 mg/kg)	38.7±0.1	43.4±0.1	38.1±0.3	43.3±0.4	38.4±0.1	42.4±0.2
Propranolol (10 mg/kg)	38.8±0.1	43.2±0.1	38.1±0.2	43.7±0.3	38.2±0.2	41.9±0.3
Nadolol	38.5±0.1	43.8±0.1	38.3±0.2	44.8±0.2	37.9±0.2	42.5±0.3
Labetalol	38.4±0.2	43.2±0.1	37.3±0.3	42.9±0.3	38.4±0.1	42.2±0.2

Values are means ± SE.

40.5 or 41.0°C, RR in each group began to drop; this decrease continued until death.

Although respiratory volume was not quantified, the measurement of RR resulted in a recorded waveform that provided an indication of degree of chest movement (22). Between 38.5 and 42.5°C, animals exhibited the following percent increases in the waveform amplitude caused by chest wall displacement during inspiration: 2 mg/kg propranolol, 81 ± 12; 10 mg/kg propranolol, 93 ± 19; nadolol, 95 ± 24; labetalol, 56 ± 14; and saline, 70 ± 12%. There were no significant differences among the groups.

DISCUSSION

Survival times and temperatures. The "shocklike" state (manifested in the drastic reduction in MAP) resulting from severe heating may be analogous in some respects to hemorrhagic shock. In particular, hyperthermia has been linked with a hemorrhagic shock syndrome in infants. In addition, Kielblock et al. (26) have described the functional hypovolemia due to heating in anesthetized rats. Therefore, some of the current discussion focuses on previous studies dealing with certain aspects of hemorrhagic shock.

In the present study, animals treated with either dose of propranolol (2 or 10 mg/kg) or labetalol died at lower T_c than saline-treated animals. Only the high dose of propranolol, however, resulted in a lower survival time. (The major difference in physiological responses among this group and the others was seen in RR, which will be discussed below.) Only labetalol treatment resulted in a lower rate of temperature rise. [On the basis of previous studies, the dose of labetalol approximated the averaged equivalent β-adrenergic blockade activity of the two propranolol doses (25).]

Animals with experimentally induced shock have survived longer under ketamine anesthesia than with other anesthetics (44). It is possible that survival time could have been shorter in the present study if other anesthetics had been used. Shorter survival time could have affected differences in physiological parameter changes among groups.

Although alteration of the blood-brain barrier due to MW has been reported, Lin and Lin (29) found that brain temperatures in rats must exceed 42°C for an appreciable length of time to cause changes in blood-brain permeability. Thus, in the present experiments, the ability of nadolol to traverse the blood-brain barrier was probably unaffected by MW exposure. The lack of effects of nado-
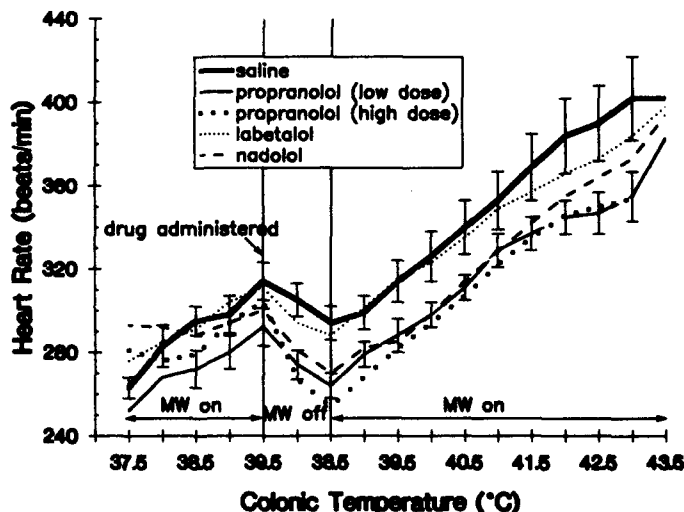

FIG. 3. Effects of adrenergic blocking agents on heart rate changes during exposure to microwaves. After initial exposure period, in which each animal's colonic temperature was raised to 39.5°C, 1 of the agents was administered. After colonic temperature returned to 38.5°C, microwave radiation (MW) was then continued until death. Heart rate measurements were recorded at every half-degree temperature increment. Nos. of animals in each group are given in Figs. 1 and 2. SEs are shown for saline group and, at selected points (where there is no overlapping between groups), for low-dose propranolol group.
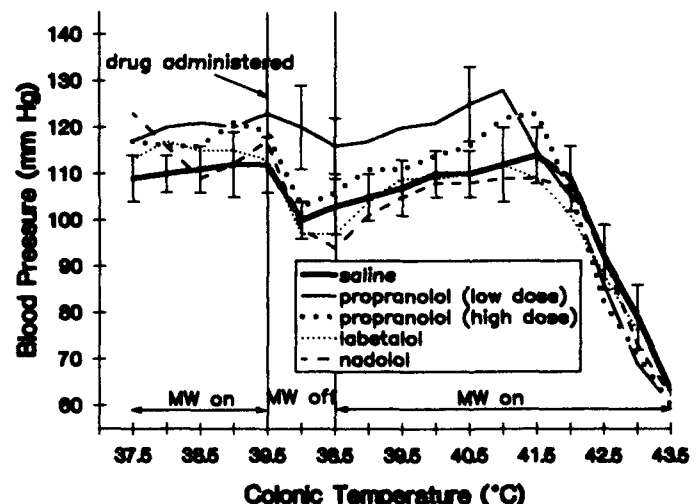

FIG. 4. Effects of adrenergic blocking agents on mean arterial blood pressure during exposure to microwaves. (Experimental procedures are explained in Fig. 3 legend.) SEs are shown for saline group and, at selected points (where there is no overlapping between groups), for low-dose propranolol group.
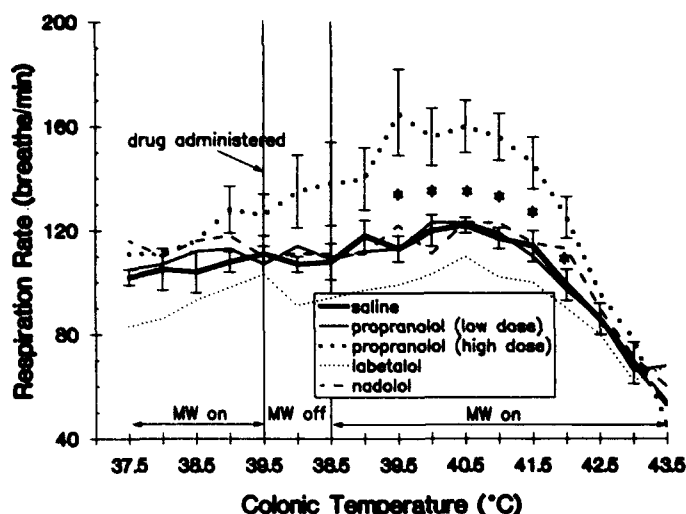
FIG. 5. Effects of adrenergic blocking agents on respiratory rate during exposure to microwaves. (Experimental procedures are explained in Fig. 3 legend.) SEs of mean are shown for saline group and, at selected points (where there is no overlapping between groups), for high-dose propranolol group. * Significant difference between saline and high-dose propranolol groups.

lol on survival time and lethal temperature in the present experiments, coupled with its poor ability to traverse the blood-brain barrier, suggests that central β-adrenergic stimulation rather than peripheral stimulation may alter thermoregulation. It is still possible, however, that a higher dose of nadolol could have affected temperature changes. [The dose used in these experiments was selected because previous studies showed that administration of nadolol at one-half of that level affected body temperature in the rat (6).]

HR and blood pressure. Both initial and peak HRs in the present study were substantially lower than in other studies of acute thermal stress in the rat. Many of the previous studies used pentobarbital or ether as an anesthetic instead of ketamine. Ketamine is an excitatory anesthetic and may cause an increase in HR in several species, including dogs and humans. In rats, however, administration of ketamine has been shown to result in decreased HR in Wistar (31), Fischer 344 (9), and Sprague-Dawley strains (18).

β-Adrenergic blockade can cause decreased HR in animals exposed to thermal stress (42). In the present experiments, after the initial MW exposure period, animals given either dose of propranolol displayed significantly greater decreases in HR (10 and 16%) compared with saline-treated animals (6%). During the terminal exposure period, however, no differences in HR change were observed among the different groups of animals.

Animals treated with nadolol exhibited a slightly greater drop in HR before terminal exposure than saline-injected animals did, but the decrease was not as great as in the two propranolol-treated groups.

In several groups, there were slight increases in MAP during the initial MW exposure period. Part of the decline in MAP after the administration of saline or antagonist could have been related to the lack of MW exposure (and concurrent heating) during this period of time. MAP in some groups, however, decreased to levels below

preexposure levels (including a decrease of ~10 mmHg in the saline group). The small volume injected is unlikely to have resulted in any effect. Although preheating in rodents can alter subsequent cardiovascular responses to heating, this effect generally occurs no earlier than 6 h after heating at 42.5°C for 1 h (39). It is still possible, however, that the initial heating period in the present experiments may have influenced the MAP response to subsequent heating.

We previously reported increased HR in rats exposed to MW (9, 19–23). During terminal exposures of anesthetized rats to 2.8-GHz (20) and 5.6-GHz MW (23), the pattern of HR and MAP changes was similar to the pattern observed by other investigators during experiments of lethal environmental heat stress in anesthetized rats (26). The present experiments showed a comparable pattern, with a gradual rise in HR throughout the entire exposure period and an increase in MAP until T_c of 41°C; after this point a significant decrease in MAP occurred. (Although MAP at 41.0°C was essentially at or only slightly above preheating control levels, this level was greater than the initial starting point during the final exposure.) Takamata et al. (41) noted that, in anesthetized rats exposed to thermal stress, HR continued to increase while MAP started to decrease at core temperatures above 43°C. They suggested that the sudden drop in MAP might have resulted from a dysfunction in the peripheral circulation and a reduction in venous return but not cardiac failure. This may also be the mechanism behind the decrease in MAP in MW-heated rats.

In propranolol-treated animals in a previous study (20), a rapid fall in MAP occurred at T_c between 40.5 and 41.0°C. In the present experiments, at T_c above 41°C, both propranolol-treated groups of animals exhibited significantly greater decreases in MAP (relative to values at the start of terminal exposure) than did other groups. However, there were no significant differences among absolute values.

The hemodynamic effects of labetalol may vary widely from one experimental situation to another depending on the balance of autonomic influences. The lack of effects (relative to saline) of 10 mg/kg of labetalol on HR in the present study is consistent with results of Brittain and Levy (2). These authors also reported that doses of labetalol as low as 0.3 mg/kg iv caused antagonism of vasopressor responses to sympathetic nerve stimulation. Despite the lack of effects of labetalol (10 mg/kg) on HR or MAP in the present experiments, animals treated with the drug exhibited a significantly lower lethal temperature than the saline group. Because of a significantly slower rate of temperature rise, however, the animals survived longer than those of the other groups. The cause of this phenomenon is unknown.

Respiration. Compared with other physiological or behavioral responses, threshold core temperatures required to bring about an increased RR in rodents are relatively high (11). In the present experiments, RR in animals treated with the high dose of propranolol was higher than in the other groups during most of the MW exposure period. During heating, one would expect hyperventilation to increase heat dissipation. In this case, however, the increased RR could have been associated

with the lower survival time in these animals. Other parameters related to lung function and perfusion were not measured in the present experiments. It is possible that, in addition to its effect on RR, propranolol could have an adverse effect on other parameters. The following previous studies support this possibility.

The analogy between severe heating and hemorrhagic shock was mentioned above. Nagy et al. (32) reported that an increase in functional residual capacity of the lungs can occur during hemorrhagic shock and could have an adverse effect on maintenance of sufficient ventilation. These authors noted that thoracic blood volume decreases considerably during hypovolemia and hypothesized that part of the increase in functional residual capacity could be due to a replacement of blood by gas in the thoracic cavity. They also hypothesized that tonic contraction of external intercostal muscles could develop because of the combination of an increased functional demand due to hyperventilation and an insufficient blood supply with resultant lactic acidosis in the muscles. Nagy et al. postulated that these factors could result in a failure of the respiratory system to maintain an adequate level of ventilation in the late stages of shock. Martins et al. (30) showed that adrenergic activation after hemorrhage could have a protective effect on the respiratory system. These investigators suggested that the decrease in pulmonary vascular volume that occurs due to acute hemorrhage would be more severe in propranolol-treated animals. This process also could have occurred in the high-dose propranolol-treated animals in the present experiments.

Although β-adrenergic stimulation can result in an increased RR in dogs (17), another study showed that blockade due to propranolol resulted in rapid and shallow breathing in guinea pigs (38). Acute administration of propranolol results in diminished oxygen uptake kinetics in men (8) and a reduction in oxygen delivery in lambs (7). Hughson (16) estimated that a decrease in mixed oxygen content could account for ~25% of the increased oxygen deficit seen during β-adrenergic receptor antagonism in exercising men. The effects of propranolol on oxygen uptake kinetics in the rat have not been adequately studied.

The decrease in maximal oxygen uptake caused by propranolol in human subjects has been postulated to be due to a central response rather than to a blockade of peripheral β-adrenergic receptors (40). Maximal expiratory flow at 50% vital capacity was significantly lower in humans given propranolol (3). Joyner et al. (24) found that, in men performing heavy exercise, β-adrenergic blockade caused increased RR but blunted increases in tidal volume, making respiration less efficient. Propranolol has been shown to increase dynamic lung resistance in anesthetized rats as well (1).

Using the dog as a model, Nelson and Swan (33) reported that survivors of hemorrhage had a lower respiratory rate than those that died; they suggested that hyperventilation may be detrimental because of consumption of large amounts of energy, which, under the circumstances, would be in short supply. Hubbard et al. (15) have hypothesized that energy depletion may be relevant to the pathophysiology of heatstroke. In addition, Nagy

et al. (32) have postulated that altered contraction of respiratory muscles (as mentioned above) may affect energy balance and may have a role in survival.

These data suggest that the role of respiration in increased susceptibility to MW-induced heating in propranolol-treated animals deserves closer scrutiny. These results could advance the understanding of the pathophysiology of heatstroke.

Summary. In summary, during MW exposure, lethal temperatures in labetalol- and propranolol-treated (2 and 10 mg/kg) rats were significantly lower than in saline controls. Survival time was significantly less only in the high-dose propranolol group. HR and MAP responses during MW exposure in all groups of animals were similar to those that occur during environmental heat stress. These parameters did not differ greatly among the groups. RR, however, was notably higher in animals treated with 10 mg/kg of propranolol. This difference in respiration may have been associated with the significantly shorter survival time in these animals.

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